**Criteria Grid**
**Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C**

| | |
|---|---|
| **Best Practice/Intervention:** | Huang TS. et al. (2013) A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis-related hepatocellular carcinoma. *Journal of Viral Hepatitis*, 20(10):729-743. |
| **Date of Review:** | February 15, 2015 |
| **Reviewer(s):** | Christine Hu |

**Part A**

| | |
|---|---|
| ***Category:*** | **Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐<br>**Social Science** ☐ **Programmatic Review** ☒ |
| ***Best Practice/Intervention:*** | **Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other: hepatitis B, hepatocellular carcinoma**<br>**Level:** **Group** ☒ **Individual** ☐ **Other:** ____<br>**Target Population: patients with viral hepatitis-related hepatocellular carcinoma**<br>**Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** ____<br>**Country of Origin: Taiwan**<br>**Language:** **English** ☒ **French** ☐ **Other:** ____ |

**Part B**

| | YES | NO | N/A | COMMENTS |
|---|---|---|---|---|
| *Is the best practice/intervention a meta-analysis or primary research?* | ☒ | ☐ | ☐ | meta-analysis; systematic review to assess the effects of adjuvant interferon therapy on survival outcomes in patients with viral hepatitis-related hepatocellular carcinoma |
| *The best practice/intervention has utilized an evidence-based approach to assess:* | | | | |
| *Efficacy* | ☒ | ☐ | ☐ | Primary outcome: recurrence-free survival and overall survival |
| *Effectiveness* | ☐ | ☒ | ☐ | |
| *The best practice/intervention has been evaluated in more than one patient setting to assess:* | | | | |

| | | | | |
|---|---|---|---|---|
| *Efficacy* | ☒ | ☐ | ☐ | 9 randomized trials included 942 participants |
| *Effectiveness* | ☐ | ☒ | ☐ | |

| | YES | NO | N/A | COMMENTS |
|---|---|---|---|---|
| *The best practice/intervention has been operationalized at a multi-country level:* | ☒ | ☐ | ☐ | Most of the included trials were conducted in Asia including five performed in Japan |
| *There is evidence of capacity building to engage individuals to accept treatment/diagnosis* | ☐ | ☐ | ☒ | |
| *There is evidence of outreach models and case studies to improve access and availability* | ☐ | ☐ | ☒ | |
| *Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?* | ☒ | ☐ | ☐ | Clear methodology |
| *Are the best practices/methodology/results described applicable in developed countries?* | ☒ | ☐ | ☐ | Similar analysis can be made with same inclusion criteria |
| *Are the best practices/methodology/results described applicable in developing countries?* | ☒ | ☐ | ☐ | |
| *Evidence of manpower requirements is indicated in the best practice/intervention* | ☐ | ☒ | ☐ | |
| *Juried journal reports of this treatment, intervention, or diagnostic test have occurred* | ☒ | ☐ | ☐ | *Journal of Viral Hepatitis* |
| *International guideline or protocol has been established* | ☐ | ☒ | ☐ | |
| *The best practice/intervention is easily accessed/available electronically* | ☒ | ☐ | ☐ | Free for download from http://onlinelibrary.wiley.com |
| *Is there evidence of a cost effective analysis? If so, what does the evidence say?* ***Please go to Comments section*** | ☐ | ☒ | ☐ | |
| *How is the best practice/intervention funded?* ***Please got to Comments section*** | ☒ | ☐ | ☐ | The research was supported by an institutional grant of Academia Sinica to PJ Chen and an institutional grant of Chang Gung Memorial Hospital, Keelung Branch |

| | | | | |
|---|---|---|---|---|
| | | | | to TS Huang |
| *Other relevant information:*<br>_____ | ☐ | ☐ | ☐ | - Adjuvant interferon therapy improves recurrence-free survival and overall survival among patients with BCV or HCV related hepatocellular carcinoma following curative treatment |

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# A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis-related hepatocellular carcinoma

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SUMMARY. The efficacy of adjuvant interferon treatment for the management of patients with viral hepatitis-related hepatocellular carcinoma (HCC) following curative treatment is controversial. We have conducted a systematic review with meta-analysis to assess the effects of adjuvant interferon therapy on survival outcomes. Randomized and nonrandomized studies (NRSs) comparing adjuvant interferon treatment with the standard of care for viral hepatitis-related HCC after curative treatment were included. CENTRAL, Medline, EMBASE and the Science Citation Index were searched with complementary manual searches. The primary outcomes were recurrence-free survival (RFS) and overall survival (OS). Nine randomized trials and 13 NRSs were included in the meta-analysis. These nine randomized trials included 942 participants, of whom, 490 were randomized to the adjuvant interferon treatment group and 452 to the control group. The results of meta-analysis showed unexplained heterogeneity for both RFS and OS. The 13 NRSs included 2214 participants, of whom, 493 were assigned to the adjuvant interferon treatment group and 1721 to the control group. The results of meta-analysis showed that, compared with controls, adjuvant interferon treatment significantly improved the RFS [hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.52–0.84, $I^2$ = 29%] and OS (HR 0.43, 95% CI 0.34–0.56, $I^2$ = 0%) of patients with hepatitis C virus-related HCC following curative treatment. There was little evidence for beneficial effects on patients with hepatitis B virus-related HCC. Future research should be aimed at clarifying whether the effects of adjuvant interferon therapy are more prominent in hepatitis C patients with sustained virological responses.

*Keywords:* adjuvant therapy, hepatocellular carcinoma, interferon, liver cancer, meta-analysis, viral hepatitis.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death worldwide, and its incidence has continuously increased over the past two decades [1,2]. Early detection of asymptomatic HCC followed by surgical resection, ablation therapy or liver transplantation offers patients a better chance of long-term survival [2–5]. However, the annual recurrence rate of HCC after curative treatment is approximately 15–20% and reaches 80–90% in the fifth year [6]. In addition, the overall 5-year survival rate after surgical resection ranges from 30% to 40%, and most patients die of intrahepatic tumour recurrence [3,4,6,7]. Therefore, it is very important that we develop an understanding on the prevention of HCC recurrence after curative treatment to ensure long-term survival benefits.

Several studies have shown that chronic viral hepatitis, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, leads to chronic inflammation in liver parenchyma, hepatocyte damage and liver regeneration. Viral hepatitis-related chronic liver diseases are associated with an increased risk of hepatocarcinogenesis and postoperative recurrence in the remnant liver [8,9]. Interferon-α is an antiviral cytokine that has long been used clinically to treat chronic HBV and HCV infections. In addition, interferon-α has been demonstrated to have antiproliferative,

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NOS, Newcastle–Ottawa Scale; NRS, nonrandomized study; RCT, randomized controlled trial; SVR, sustained virological response.

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immunomodulatory and antiangiogenic effects on human cancers [10,11]. Thus, interferon-$\alpha$ has been proposed to have anticancer effects and to reduce or delay recurrence after curative treatment of HCC.

Earlier randomized controlled trials (RCTs) exploring adjuvant interferon therapy for patients with HCV-related HCC after curative treatment have reported promising improvement in recurrence-free survival [12–14]. However, two large RCTs failed to confirm the efficacy of adjuvant interferon therapy for recurrence-free survival and overall survival in patients with viral hepatitis-related HCC after curative treatment [15,16]. Although several systematic reviews and meta-analyses suggested that adjuvant interferon therapy significantly improved recurrence-free survival and overall survival, the routine administration of adjuvant interferon treatment in these populations is still controversial [17–22]. To appropriately evaluate the efficacy of adjuvant interferon therapy (compared with standard of care treatment) on the survival outcomes of patients with viral hepatitis-related HCC following curative treatment, we have performed a comprehensive systematic review of the clinical evidence.

## MATERIALS AND METHODS

### *Search strategy*

This prospective review was conducted according to our registered protocol, which included plans for data analysis as well [23]. Our selection process for determining the inclusion of studies was not restricted by language, publication status or date. The search terms used were HCC, hepatic tumour, liver cancer, liver tumour, interferon, peginterferon, pegylated interferon, viraferonpeg, pegintron and pegasys. We combined the exploration of MeSH descriptors with the application of Boolean operators. We searched the following databases: CENTRAL (the Cochrane Library, latest issue May 2012), MEDLINE (January 1950–May 2012), EMBASE (January 1980–May 2012) and the Science Citation Index (January 1981–May 2012). The MEDLINE search strategy is described in Appendix 1. To identify relevant trials, we also searched the reference lists of systematic reviews and databases of clinical trials (http://www.clinicaltrials.gov/).

### *Inclusion criteria*

We included articles on RCTs and nonrandomized studies (NRSs) comparing adjuvant interferon therapy with controls in patients after curative treatment for viral hepatitis-related HCC. We included NRSs for two reasons. First, adjuvant interferon therapy studies cannot be blinded and can have several adverse effects; therefore, well-conducted NRSs might offer evidence that is comparable with the results of RCTs [24]. Second, we were able to obtain subgroup information (e.g. information on the sustained virological responses [SVRs] group) from NRSs involving patients with HCV infections. This information would only be available if we were able to conduct individual patient data meta-analysis of RCTs. We included trials that compared adjuvant interferon therapy to standard of care treatment after curative treatment (e.g. surgery or ablation) for viral hepatitis-related HCC. Our primary outcomes were recurrence-free survival and overall survival.

### *Selection of studies and data extraction*

Three authors (TSH, YCS and JNS) independently screened the titles, abstracts and full texts of trials identified in the literature search. Two authors (TSH and YCS) independently extracted the data and assessed the trial quality. A third author (SSY) was consulted to resolve disagreements and for quality assurance. We used a predesigned standard form to extract the following information: characteristics of the study (study settings, study designs, methods of randomization and methods for adjusting confounding factors), characteristics of participants and diseases, interventions (type of interferon, dose and duration) and outcomes (survival outcomes and adverse events).

### *Assessment of risk of bias in the included studies*

We adjudicated the methodological quality of the included RCTs using the risk of bias tool suggested by the Cochrane Handbook for Systematic Reviews of Interventions [25]. The risk of bias tool for RCTs uses a domain-based evaluation method that includes the following risk of bias domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting). In addition, we assessed the methodological quality of NRSs using the Newcastle–Ottawa Scale (NOS) [26]. The NOS includes three parts: selection scores (representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study, with one point for each item); comparability scores (comparability of cohorts based on the design or analysis, with a maximum of two points); and outcome scores (assessment of outcome, determination of whether follow-up was long enough for outcomes to occur and adequacy of follow-up of cohorts, with one point for each item). We defined 'high quality' as an NOS of $\geq 8$ points and 'moderate quality' as NOS between 5 and 7 points.

### *Data synthesis and statistical analysis*

In literature-based meta-analyses, the hazard ratio (HR), which takes into account the number and timing of

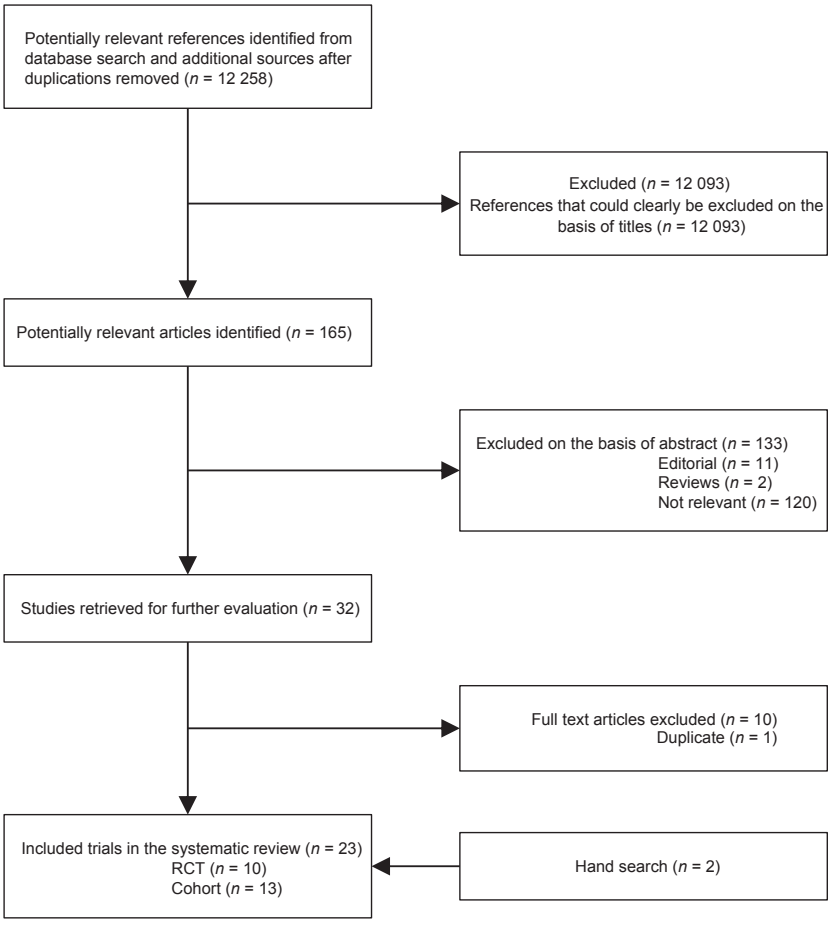


**Fig. 1** Flow diagram of the article selection process.

events as well as censorship, provides the most appropriate effect size for time-to-event outcomes [27]. Thus, we extracted HRs with confidence intervals (CIs) (if available) from individual studies to estimate the summary effects. If these data were not available, we attempted to estimate the summary effects by applying the methods suggested by Parmar *et al.* [27]. The calculations were performed using a spreadsheet developed by Tierney *et al.* [28]. Among HCV-infected patients, the survival outcomes of SVR groups were also extracted from individual NRSs (if reported). We pooled the summary effect size with random-effects meta-analysis [29]. Statistical heterogeneity was assessed using the $I^2$ statistic and the $Q$ statistic with the chi-square test where $I^2 \leq 25\%$ indicates low heterogeneity, $25\% < I^2 < 50\%$ indicates moderate heterogeneity and $I^2 \geq 50\%$ indicates large heterogeneity [30,31]. We explored the clinical heterogeneity using subgroup analyses based on type of viral hepatitis, treatment duration and study quality. We performed data synthesis and statistical analysis using Review Manager (RevMan Version 5.1; The Nordic Cochrane Center, Copenhagen, Denmark). For statistical analysis, the significance level was established at 0.05.

## RESULTS

### *Search results and study characteristics*

Figure 1 summarizes the literature search results. We excluded 10 references after a comprehensive review of the full texts. We detailed the reasons for exclusion in Table S1. We included 10 RCTs [14,15,17,32–38] and 13 NRSs [39–51]. Table 1 outlines the key characteristics of the included RCTs. Most of the included trials were conducted in Asia including five that were performed in Japan. Miyaguchi *et al.* enrolled patients that developed HCC post-HCV clearance; however, because of variation in inclusion criteria compared with other RCTs and the efficacy of the curative treatment strategy, we excluded this study from data synthesis. Five RCTs recruited patients with HCV-related HCC, whereas three RCTs recruited mostly HBV-related HCC ($\geq 80\%$). One study enrolled both HCV- and HBV-related HCC patients. The inclusion/exclusion criteria, curative treatment strategies, interferon administration schedule and reported SVRs varied between the studies. Table 2 outlines the key characteristics of the included cohort studies, which were all conducted in Asia (most

**Table 1** Randomized controlled trials included in the systematic review of the effects of adjuvant interferon treatment on patients with viral hepatitis-related HCC following curative treatment

| References, site | Age, years, [median (range)] or [mean (SD)] | No. of Male/No. of total patients | Inclusion/exclusion criteria | Treatment strategy | No. of patients with SVRs/No. of patients evaluated (%) | Instances of discontinuation because of AEs |
|---|---|---|---|---|---|---|
| Ikeda *et al.* [12], Japan, single centre | T: 60 (54–70)<br>C: 64.5 (51–69) | T: 7/10<br>C: 6/10 | Inclusion criteria: HCV-related HCC after curative treatment (resection or PEIT).<br>Exclusion criteria: concomitant HBV infection, decompensated liver disease | Natural IFN-beta, 6 MU twice per week for 36 months | 0 | 1 |
| Kubo *et al.* [32], Japan, two centres | T: 61.9 (5.8)<br>C: 62.3 (5) | T: 15/15<br>C: 15/15 | Inclusion criteria: HCV-related HCC (single tumour <5 cm) after curative treatment (resection), Child-Pugh A or B cirrhosis.<br>Exclusion criteria: concomitant HBV or HIV infection, severe thrombocytopenia | IFN-alpha, 6 MU per day for 2 weeks, then 3 times per week for 14 weeks and finally twice per week for 88 weeks.<br>Mean time to IFN therapy: 9 weeks | 2/15 (13.3%) | 3 |
| Miyaguchi *et al.* [33], Japan, single centre | T: 66.2 (7.4)<br>C: 65.0 (7.1) | T: 10/16<br>C: 7/16 | Inclusion criteria: Occurrence of HCC post-HCV clearance and after curative treatment (TAE, PEIT, or both).<br>Exclusion criteria: concomitant HBV infection, candidate for surgery, diffuses HCC | IFN-alpha-2b, 3 MU twice per week for 4 months with a cumulative MU of 104.<br>Time to IFN therapy: within 3 weeks | 11/22 (50%) | NR |
| Shiratori *et al.* [34], Japan, single centre | T: 61 (37–70)<br>C: 63 (51–69) | T: 35/49<br>C: 17/25 | Inclusion criteria: HCV-related HCC with $\leq 3$ tumours after curative treatment (PEIT), compensated cirrhosis, age $\leq 70$ years, no previous IFN treatment.<br>Exclusion criteria: concomitant HBV infection, primary biliary cirrhosis, severe comorbidity, Child-Pugh B or C cirrhosis | Natural IFN-alpha, 6 MU 3 times per week for 48 weeks. Reduced to 3 MU if intolerable. Stopped IFN if HCV RNA (+) was observed after 24 weeks of IFN treatment.<br>Time to IFN therapy: 2–3 months | 14/49 (29%) | 9 |

(continued)

Table 1 *(continued)*

| References, site | Age, years, [median (range)] or [mean (SD)] | No. of Male/No. of total patients | Inclusion/exclusion criteria | Treatment strategy | No. of patients with SVRs/No. of patients evaluated (%) | Instances of discontinuation because of AEs |
|---|---|---|---|---|---|---|
| Lin *et al.* [14], Taiwan, single centre | T 1: 60 (26–70)<br>T 2: 63 (31–65)<br>C: 59 (49–72) | T1: 10/11<br>T2: 6/9<br>C: 7/10 | Inclusion criteria: HCV or HBV-related HCC (including secondary recurrence) after curative treatment (PEIT or PEIT + TAE).<br>Exclusion criteria: Child-Pugh C cirrhosis, platelet count <50 000/mm$^3$ | Continuous IFN-alpha-2b, 3 MU 3 times per week for 24 months.<br>Intermittent IFN–alpha-2b, 3 MU daily for 10 days every month for 6 months followed by 3 MU daily for 10 days every 3 months for an additional 18 months | NR | 2 |
| Mazzaferro *et al.* [15], Italy, four centres | HCV+, anti-HBc−<br>T: 65 (45–74)<br>C: 67 (50–73)<br>HCV+, anti-HBc+<br>T: 65 (41–73)<br>C: 67 (36–72) | HCV+, anti-HBc−<br>T: 35/42<br>C: 26/38<br>HCV+, anti-HBc+<br>T: 26/34<br>C: 25/36 | Inclusion criteria: HCV-related HCC after curative treatment (resection), preresection treatments (TAE, RFA, PEIT), age 18–75 years.<br>Exclusion criteria: HBsAg (+), any other neoplasm, previous IFN or chemotherapy of other tumours, severe surgical complications, co-morbidity, active alcohol intake | IFN-alpha-2b, 3 MU 3 times per week for 48 weeks.<br>Time to IFN therapy: within 6 weeks post-resection | 2/28 (7%) | 6 |
| Sun *et al.* [36], China, single centre | T: 52.2<br>C: 50.4 | T: 106/118<br>C: 102/118 | Inclusion criteria: HBV-related HCC after curative treatment (resection), bilirubin <34 mM.<br>Exclusion criteria: HCV (+), platelet count <40 000/mm$^3$, leukocyte count <2500/mm$^3$ | IFN-alpha-1b, 3 MU twice per week for 2 weeks, then 5 MU 3 times per week for 18 months.<br>Time to IFN therapy: within 4–6 weeks | NA | 11 |

(continued)

Table 1 *(continued)*

| References, site | Age, years, [median (range)] or [mean (SD)] | No. of Male/No. of total patients | Inclusion/exclusion criteria | Treatment strategy | No. of patients with SVRs/No. of patients evaluated (%) | Instances of discontinuation because of AEs |
|---|---|---|---|---|---|---|
| Lo *et al.* [37], Hong Kong, single centre | T: 49 (26–75)<br>C: 54 (24–74) | T: 31/40<br>C: 34/40 | Inclusion criteria: HBV- or HCV-related HCC after curative treatment (resection), age 18–75 years.<br>Exclusion criteria: previous chemotherapy, immunotherapy, psychiatric illness, poor hepatic function, poor performance status, platelet count <75 000/mm$^3$, neutrophil count <1500/mm$^3$ | IFN-alpha 2b, 10 MU 3 times per week for 16 weeks.<br>Time to IFN therapy: 60 days after surgery | NA | 3 |
| Chen *et al.* [16], Taiwan, multi-centres | T: 50 (48–54)<br>C: 49 (46–51) | T: 108/133<br>C: 112/135 | Inclusion criteria: HBV- or HCV-related HCC after curative treatment (resection), Child-Pugh A cirrhosis, good bone marrow reserve.<br>Exclusion criteria: age >70 years, vascular involvement in radiography, ECOG performance score >2 | IFN-alpha 2b, dose escalation from 1 to 5 MU in the first week and then maintained at 5 MU 5 times per week for 4 weeks, subsequently reducing to 3 times per week for an additional 48 weeks.<br>Time to IFN therapy: within 6 weeks after surgery | 2/15 (13.3%) | 5 |
| Ishikawa *et al.* [38], Japan, single centre | T: 65.6 (7.9)<br>C: 72.6 (6.6) | T: 21/29<br>C: 13/25 | HCV-related HCC stage I/II after curative treatment | IFN-alpha-2b, 1.5 $\mu$g/kg body weight per week with RBV | 10/29 (34.5%) | NR |

AE, adverse effect; anti-HBc, hepatitis B anticore antibody; C, control group; DNA, deoxyribonucleic acid; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; MU, million units; NA, not applicable; NR, not reported; PEIT, percutaneous ethanol injection therapy; RBV, ribavirin; RFA, radiofrequency ablation; RNA, ribonucleic acid; SD, standard deviation; SVR, sustained virological response; T, treatment group; TAE, transcatheter arterial chemoembolization.

**Table 2** Nonrandomized studies included in the systematic review of the effects of adjuvant interferon treatment on patients with viral hepatitis-related HCC following curative treatment

| References | Cohort formation | Duration of follow-up | Age, years, [median (range)] or [mean (SD)] | No. of males (%) | SVR (%) | Adjustment |
|---|---|---|---|---|---|---|
| Suou *et al.* [39] | From October 1990 to March 1998, a prospective hospital-based cohort study was performed in Japan. Anti-HCV Ab (+), HBsAg (−) patients underwent resection or PEIT followed by treatment with IFN-alpha for 24 weeks, which was started 1–3 months after curative treatment. The study recruited 988 patients. T = 18/C = 22 were analysed. There were no instances of discontinuation because of AEs | NR | T: 61 (6)<br>C: 62 (4) | T: 15 (83.3)<br>C: 18 (81.8) | 33.3 | Tumour factors |
| Hung *et al.* [40] | From January 1998 to December 2002, a retrospective hospital-based cohort study was performed in Taiwan. HCV RNA (+), HBsAg (−) patients underwent PTA, PEIT, MCT, TAE or a combination of these followed by IFN + RBV treatment for 24–48 weeks. The study recruited 609 patients. T = 16/C = 33 were analysed. There were 4 instances of discontinuation because of AEs | <3 years | T: 62.6 (8.0)<br>C: 63.1 (8.5) | T: 15 (75)<br>C: 30 (75) | 50 | None |
| Sakaguchi *et al.* [41] | From June 1999 to August 2003, a retrospective hospital-based cohort study was performed in Japan. Patients with HCV-related HCC underwent RFA and treatment with IFN-alpha-2b for as long as possible (median 1.8 years). The study recruited 141 patients. T = 24/C = 33 were analysed. There were no instances of discontinuation because of AEs | T: 2.3 years<br>C: 1.9 years | T: 69 (9.2)<br>C: 67 (9.7) | T: 17 (70.8)<br>C: 24 (72.7) | 4.2 | Gender, tumour size, number of tumours, platelet count, AFP, PIVKA II level, ALT |
| Akamatsu *et al.* [42] | From January 1993 to February 2004, a retrospective hospital-based cohort study was performed in Japan. HCV RNA (+), HBsAg (−) patients underwent resection or ablation and treatment with IFN-alpha for 24–48 weeks beginning within 2–3 months. The study recruited 1306 patients. T = 53/C = 399 were analysed | NR | SVR: 59 (57–68)<br>Non-SVR: 61 (37–75)<br>Non-IFN: 68 (41–86) | T: 38 (71.7)<br>C: 271 (67.9) | 32 | Age, gender, total bilirubin, tumour factors, AFP |
| Someya *et al.* [43] | From 1980 to 2003, retrospective hospital-based cohort study was performed in Japan. Patients with anti-HCV Ab (−), HBsAg (+) and liver cirrhosis underwent resection and treatment with IFN-alpha for 6 months or longer. The study recruited 210 patients. T = 11/C = 69 were analysed | T + C: 16.2 years | T: 50 (41–60)<br>C: 52 (31–72) | T: 11 (100)<br>C: 58 (84) | NA | AST, HBV DNA, age |

(continued)

Table 2 *(continued)*

| References | Cohort formation | Duration of follow-up | Age, years, [median (range)] or [mean (SD)] | No. of males (%) | SVR (%) | Adjustment |
|---|---|---|---|---|---|---|
| Kudo *et al.* [44] | From June 1999 to May 2006, a retrospective hospital-based cohort study was performed in Japan. Patients with HCV genotype 1b underwent RFA and maintenance IFN therapy for a median of 4.7 years (1.0–7.1) beginning 2 months after curative treatment. The study recruited 1856 patients. T = 43/C = 84 were analysed. There were no instances of discontinuation because of AEs | T: 5.1 years<br>C: 4.9 years | T: 65 (5.3)<br>C: 66 (5.9) | T: 33 (76.7)<br>C: 60 (71.4) | 4.7 | PIVKA II level |
| Jeong *et al.* [45] | From August 2001 to December 2006, prospective hospital-based cohort study was performed in Japan examining HCV-related liver cirrhosis. HCV RNA (+), HBsAg (−) patients underwent resection or ablation and were given IFN-alpha for at least 48 weeks within 12 weeks following curative treatment. The study recruited 176 patients. T = 16/C = 16 were analysed. There were no instances of discontinuation because of AEs | T: 3.1 years<br>C: 3.8 years | T: 68.5 (53–73)<br>C: 67.5 (58–75) | T: 10 (62.5)<br>C: 11 (68.8) | 12.5 | None |
| Jeong *et al.* [46] | From March 1992 to 2004, a retrospective hospital-based cohort study was performed in Japan. HCV RNA (+), HBsAg (−) patients underwent resection or ablation and were given IFN-alpha for 24 weeks within 24 weeks following curative treatment. The study recruited 495 patients. T = 42/C = 42 were analysed. There were 3 instances of discontinuation because of AEs | T: 2.7 years<br>C: 2.6 years | T: 62 (45–69)<br>C: 63 (40–69) | T: 36 (85.7)<br>C: 29 (69.0) | 69 | Child-Pugh class, ICG R15 |
| Katagiri *et al.* [47] | Since 1990, a retrospective hospital-based cohort has been performed in Japan. HCV RNA (+) patients underwent curative resection and were given IFN-alpha 2b (10 MU for 24 weeks) or IFN-alpha 2a (6 MU for 24 weeks). T = 20/C = 182 were analysed. There were no instances of discontinuation because of AEs | T: >5 years<br>C: >5 years | T: 59.6 (4.1)<br>C: 58.8 (5.2) | T: 16 (80)<br>C: 145 (79.7) | 30 | None |
| Ikeda *et al.* [48] | From 2004 to 2006, a retrospective hospital-based cohort study was performed in Japan. Anti-HCV Ab (+), HBsAg (−) patients underwent resection or ablation and were given IFN-alpha (68) or IFN-alpha + RBV (7) for 2 years or longer. The study recruited 729 patients. T = 77/C = 302 were analysed. There were 8 instances of discontinuation because of AEs | T: 5.6 years<br>C: 4.2 years | T: 63 (43–77)<br>C: 66 (39–87) | T: 46 (59.7)<br>C: 191 (63.2) | 5.2 | ICG R15, cancer treatment, AFP, albumin, platelet count |

(continued)

Table 2 *(continued)*

| References | Cohort formation | Duration of follow-up | Age, years, [median (range)] or [mean (SD)] | No. of males (%) | SVR (%) | Adjustment |
|---|---|---|---|---|---|---|
| Qu *et al.* [49] | From 2004 to 2006, a retrospective hospital-based cohort study was conducted in China. HBV (+) patients underwent curative resection and were given IFN-alpha-1b for 18 months beginning 4–6 weeks after resection. The study recruited 1045 patients. T = 101/C = 467 were analysed. There were 4 instances of discontinuation because of AEs | T + C: 4.4 years | T: 50.98 (9.88) C: 52.65 (10.32) | T: 86 (85.1) C: 407 (87.2) | NA | Tumour size, microvascular invasion, multiple tumour nodules |
| Hagihara *et al.* [50] | From January 1997 to March 2009, a retrospective hospital-based cohort study was conducted in Japan. HCV RNA (+), HBsAg (−) patients underwent curative treatment (resection, RFA, PEIT, MCT). Fifteen patients were given IFN-alpha-2a for 22–24 weeks, and 22 patients were given IFN-alpha-2b + RBV for 22–24 weeks starting 242 days (median) after curative treatment. The study recruited 358 patients. T = 34/C = 34 were analysed. There were 3 instances of discontinuation because of AEs | T: 4.6 years C: 3.6 years | T: 63 (48–77) C: 67 (43–85) | T: 29 (78) C: 95 (65) | 51.4 | Propensity score matching (age, sex, genotype, response to IFN therapy, AFP, liver function tests, tumour factors, observation period) |
| Tanimoto *et al.* [51] | From June 2003 to 2009, a retrospective hospital-based cohort study was conducted in Japan. HCV RNA (+), HBsAg (−) patients underwent curative hepatectomy and received peg-IFN within 9 months after curative resection [genotype 1b (IFN + RBV) for 48 weeks, genotype 2 IFN for 24 weeks]. The study recruited 370 patients. T = 38/C = 38 were analysed. There were 9 instances of discontinuation because of AEs | T: 3.8 years C: 3.5 years | T: 65.5 (53–75) C: 69 (51–80) | T: 23 (60.5) C: 25 (65.8) | 42.1 | Propensity score matching (age, sex, genotype, liver function tests, tumour factors, operative factors) |

AE, adverse effect; anti-HBc, hepatitis B anticore antibody; anti-HCV Ab, anti-hepatitis C virus antibody; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, control group; DNA, deoxyribonucleic acid; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICG R15, indocyanine green retention test at 15 min; IFN, interferon; MCT, microwave coagulation therapy; MU, million units; NA, not applicable; NR, not reported; PEIT, percutaneous ethanol injection therapy; peg-IFN, pegylated interferon; PIVKA II, serum prothrombin induced by vitamin K absence or antagonist II; PTA, percutaneous tumour ablation therapy; RBV, ribavirin; RFA, radiofrequency ablation; RNA, Ribonucleic acid; SVR, sustained virological response; T, treatment group; TAE, transcatheter arterial chemoembolization.

**Table 3** HRs for the recurrence-free survival and overall survival of patients given adjuvant interferon treatment compared with controls according to meta-analysis and subgroup analysis of randomized controlled trials

| | HR (95% CI) | Test for heterogeneity | Test for interaction |
|---|---|---|---|
| Recurrence-free survival | | | |
| Overall (9 studies) | 0.75 (0.56–1.01) | **$P = 0.02$, $I^2 = 57\%$** | NA |
| Subgroup analysis according to type of viral hepatitis | | | |
| Patients with HCV (5 studies) | 0.65 (0.40–1.05) | $P = 0.06$, $I^2 = 56\%$ | $P = 0.16$ |
| Recruited $\geq 80\%$ patients with HBV (3 studies) | 0.96 (0.73–1.26) | $P = 0.23$, $I^2 = 32\%$ | |
| Overall survival | | | |
| Overall (7 studies) | 0.45 (0.25–0.80) | **$P = 0.0006$, $I^2 = 75\%$** | NA |
| Subgroup analysis according to type of viral hepatitis | | | |
| Patients with HCV (4 studies) | **0.27 (0.12–0.62)** | $P = 0.14$, $I^2 = 45\%$ | $P = 0.11$ |
| Recruited $\geq 80\%$ patients with HBV (3 studies) | 0.68 (0.32–1.45) | **$P = 0.003$, $I^2 = 83\%$** | |

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HRs, hazard ratio; NA, not applicable.
Bold values indicate large heterogeneity.

commonly in Japan). Most studies used the retrospective cohort design, and only two were prospective studies. Moreover, most studies recruited patients with HCV-related HCC, and only two studies enrolled HBV-related HCC patients. The interferon administration schedule and reported SVRs varied among the included studies. However, the included populations and curative treatment strategies were more consistent in NRSs than in RCTs. In both NRSs and RCTs, most patients were middle-aged to elderly men.

### *Quality assessment*

A summary of the risk of bias is provided for RCTs and NRSs (Tables S2 & S3, respectively). The included RCTs varied with regard to reporting of random sequence generation and allocation concealment. All the RCTs were at high risk for performance bias, and most of the included RCTs were at high risk for reporting bias. The NOS of the NRSs ranged from 5 to 9 points. Six NRSs had scores of more than eight points.

### *Meta-analysis of recurrence-free survival and overall survival data from randomized controlled trials*

Overall, all nine RCTs reported recurrence-free survival, whereas seven reported overall survival. These nine trials comprised 942 participants, of whom, 490 were randomized to the adjuvant interferon treatment group and 452 were randomized to the control group. The results of meta-analysis showed statistically significant heterogeneity for both recurrence-free survival and overall survival (Table 3; Figs S1 & S2). The results showed that most of the variability across studies was because of heterogeneity rather than chance. Therefore, we could not justifiably interpret the results by merely pooling the summary effect.

Subgroup analysis stratified by type of viral hepatitis showed that there was little evidence for improvement of recurrence-free survival among patients with HBV-related HCC who were administered adjuvant interferon treatment (Table 3 and Fig. S3). Adjuvant interferon treatment significantly improved the overall survival of patients with HCV-related HCC compared with controls (Table 3 and Fig. S4). However, there was still a moderate level of heterogeneity.

### *Meta-analysis of recurrence-free survival and overall survival data from nonrandomized studies*

Overall, 11 of 13 NRSs reported recurrence-free survival, and 11 of 13 NRSs reported overall survival. These 13 trials comprised 2214 participants, of whom, 493 were assigned to adjuvant interferon treatment and 1721 were assigned to control treatment. Adjuvant interferon treatment had a statistically significant effect on the recurrence-free survival of patients with HCV-related HCC compared with controls (HR 0.66, 95% CI 0.52–0.84; Table 4 and Fig. S5). There was moderate between-study heterogeneity ($P = 0.19$, $I^2 = 29\%$). Subgroup analyses according to treatment duration and study quality showed little evidence for interaction. Adjuvant interferon treatment had a statistically significant effect on the overall survival of patients with HCV-related HCC compared with controls (HR 0.43, 95% CI 0.34–0.56; Fig. 2), and there was little evidence of statistical heterogeneity ($P = 0.43$, $I^2 = 0\%$). Moreover, subgroup analyses according to treatment duration and study quality showed little evidence for interaction (Table 4).

Four studies provided subgroup data on the recurrence-free survival and overall survival of HCV patients who achieved SVR. Adjuvant interferon treatment had a statistically significant effect on the recurrence-free survival of SVR patients compared with controls (HR 0.60, 95% CI 0.36–0.98,

**Table 4** HRs for the recurrence-free survival and overall survival of patients given adjuvant interferon treatment compared with controls according to meta-analysis and subgroup analysis of nonrandomized studies

| | HR (95% CI) *P*-value | Test for heterogeneity | Test for interaction |
|---|---|---|---|
| Recurrence-free survival | | | |
| Subgroup analysis according to types of viral hepatitis | | | |
| Patients with HCV (9 studies) | **0.66 (0.52–0.84) *P* = 0.0007** | $P = 0.19$, $I^2 = 29\%$ | $P = 0.66$ |
| Patients with HBV (2 studies) | 0.50 (0.14–1.70) $P = 0.27$ | $P = 0.08$, $\mathbf{I^2 = 67\%}$ | |
| Subgroup analysis according to treatment duration among studies that recruited patients with HCV infections | | | |
| Treatment duration >12 months (3 studies) | **0.59 (0.42–0.84) *P* = 0.003** | $P = 0.26$, $I^2 = 26\%$ | $P = 0.48$ |
| Treatment duration $\leq$12 months (6 studies) | **0.71 (0.50–1.00) *P* = 0.05** | $P = 0.18$, $I^2 = 34\%$ | |
| Subgroup analysis according to study quality among studies that recruited patients with HCV infections | | | |
| High quality (NOS $\geq$8 points) (4 studies) | **0.71 (0.56–0.90) *P* = 0.005** | $P = 0.53$, $I^2 = 0\%$ | $P = 0.24$ |
| Moderate quality (NOS between 5 and 7 points) (5 studies) | **0.51 (0.31–0.85) *P* = 0.01** | $P = 0.08$, $\mathbf{I^2 = 52\%}$ | |
| Overall survival | | | |
| Subgroup analysis according to type of viral hepatitis | | | |
| Patients with HCV (10 studies) | **0.43 (0.34–0.56) *P* < 0.00001** | $P = 0.43$, $I^2 = 0\%$ | $P = 0.13$ |
| Patients with HBV (1 study) | 0.61 (0.42–0.89) $P < 0.009$ | NA | |
| Subgroup analysis according to treatment duration among HCV studies | | | |
| Treatment duration >12 months (3 studies) | **0.50 (0.37–0.68) *P* < 0.00001** | $P = 0.55$, $I^2 = 0\%$ | $P = 0.09$ |
| Treatment duration $\leq$12 months (7 studies) | **0.32 (0.21–0.49) *P* < 0.00001** | $P = 0.54$, $I^2 = 0\%$ | |
| Subgroup analysis according to NOS among HCV studies | | | |
| High quality (NOS $\geq$8 points) (5 studies) | **0.41 (0.28–0.59) *P* < 0.00001** | $P = 0.24$, $I^2 = 27\%$ | $P = 0.80$ |
| Moderate quality (NOS between 5 and 7 points) (5 studies) | **0.37 (0.20–0.67) *P* = 0.001** | $P = 0.43$, $I^2 = 0\%$ | |

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HRs, hazard ratio; NA, not applicable; NOS, Newcastle–Ottawa Scale.
Bold values denote significance level at 0.05.

$I^2$ = 35%; Fig. S6). Adjuvant interferon treatment also significantly improved the overall survival of SVR patients compared with controls (HR 0.60, 95% CI 0.36–0.98, $I^2$ = 35%; Fig. S7). However, the sample sizes were small for both recurrence-free survival and overall survival.

### *Publication bias*

We evaluated the publication bias of cohort studies that recruited patients with HCV-related HCC using the funnel plot. The funnel plot was symmetrical for large studies (Fig. S8). Small studies with negative effects could be missing, and if they were, the true effect could be smaller than the overall effect.

## DISCUSSION

There are a few previously published systematic reviews on this topic, but ours included more studies than theirs [17–21]. In addition, the pooling of RCTs and NRSs in some of the previous meta-analyses may not have been appropriate [25]. Furthermore, most published NRSs included patients with HCV-related HCC. The pooling of RCTs and NRSs that recruited patients with different types of viral hepatitis could lead to spurious findings that adjuvant interferon therapy improves recurrence-free survival and overall survival among patients with HBV or HCV-related HCC following curative treatment. Importantly, the mechanisms of hepatocarcinogenesis and clinical

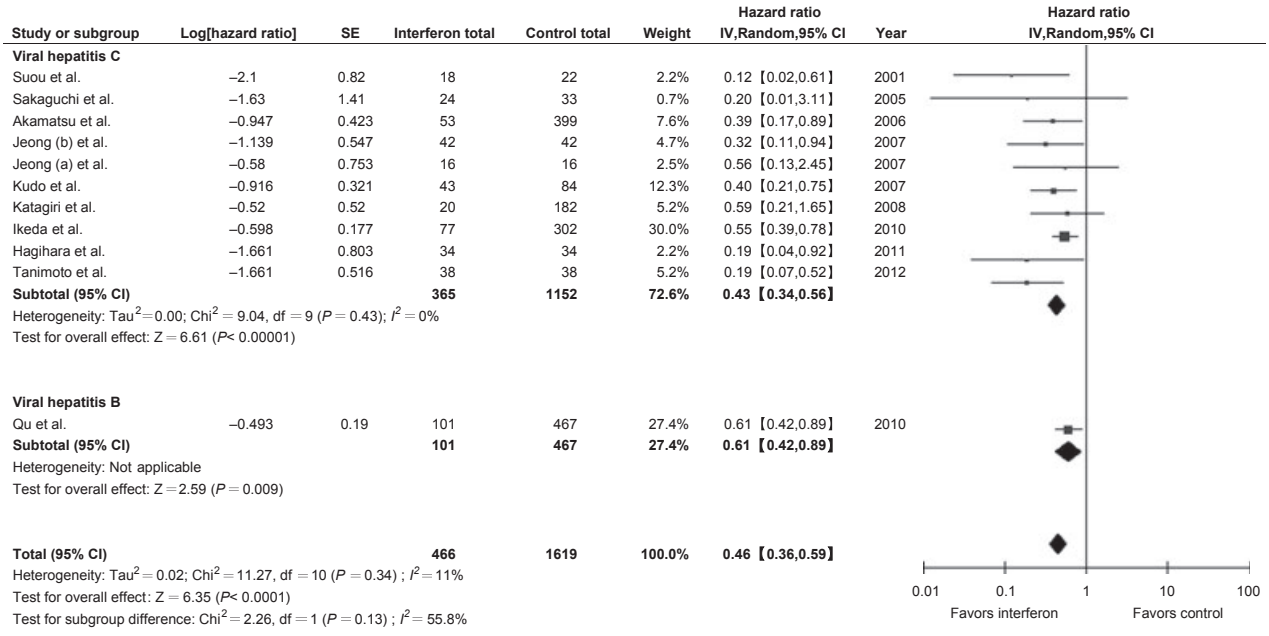


**Fig. 2** Forest plot of nonrandomized studies comparing the overall survival of patients with viral hepatitis-related hepatocellular carcinoma treated with adjuvant interferon therapy after curative treatment with that of controls. The data are stratified according to the type of viral hepatitis.

management of chronic HBV and HCV infections are different [52,53].

Nevertheless, the results of our meta-analysis of RCTs are still difficult to interpret because of unexplained heterogeneity. The results of the meta-analysis of NRSs provide evidence that compared with standard of care treatment, adjuvant interferon therapy significantly improves the recurrence-free survival and overall survival of patients with HCV-related HCC following curative treatment. Subgroup analysis according to treatment duration indicated that there is little evidence for larger effects of prolonged adjuvant interferon treatment (i.e. more than 12 months). Adjuvant interferon treatment significantly improves the recurrence-free survival and overall survival of HCV-related HCC patients who exhibit SVRs. However, only four studies provide adequate data with which to pool the summary effect.

Previous research has indicated that interferon-α may have anticancer effects [11,12]. If this is the case, interferon-α may be beneficial for patients with HCV-related HCC or HBV-related HCC. However, our meta-analysis demonstrates that there is little evidence indicating that adjuvant interferon therapy improves recurrence-free survival and overall survival among patients with HBV-related HCC. The use of adjuvant interferon treatment to prevent secondary carcinogenesis via the suppression of inflammation should be further investigated in patients with HBV-related HCC. On the other hand, our meta-analysis suggests that the current standard of care treatment for HCV infections, which employs pegylated interferon-α and ribavirin [52], should be adopted in clinical practice to treat patients with HCV-related HCC after curative treatment. The question of whether the effects of adjuvant interferon therapy are more prominent in patients with SVRs can only be answered after more clinical trials are performed.

Our meta-analysis had several advantages. First, we performed a comprehensive literature search to reduce the effect of publication bias. Second, we used the HR as the summary effect size metric for time-to-event outcomes. The HR calculated for a meta-analysis is interpreted as the relative hazard of an event occurring in the intervention group compared with its hazard of occurrence in the control group. Moreover, it can also be translated into an absolute difference in the proportion of patients who are event-free at a particular time point by assuming proportional hazards, and it can be translated into an absolute difference in the median event-free time by assuming exponential distributions. Third, we assessed the risk of bias in RCTs and NRSs with standard tools suggested in the Cochrane Handbook for Systematic Reviews of Interventions [25]. The use of such tools facilitates the conduct of subgroup analyses to detect the effect of study quality on the pooled effect. Finally, combining the effect according to the viral hepatitis type makes the results more practical.

Our meta-analysis had several limitations. First, selection bias is always a concern in NRSs, and second, confounding factors could be another source of bias. Nevertheless, interferon treatment, like surgical intervention, cannot be blinded and can have several adverse effects. Abraham *et al.* [24] have demonstrated that meta-analyses of well-designed nonrandomized comparative studies of surgical procedures are probably as accurate as those of RCTs. Third, most NRSs used a retrospective design, and retro-

spective studies inevitably have information bias. Fourth, small studies with negative effects might be missing, which could lead to an overestimation of the overall effect. However, we believe that our conclusions would not be altered by small-study effects. Finally, we cannot assess whether interferon therapy would have time-varying effects. In this situation, the proportional hazard assumptions would be violated in primary studies, and the HR would be a function of time. Most of the published studies did not address this question nor did they conduct an analysis to test the proportional hazard assumption.

Adjuvant interferon therapy significantly improves the recurrence-free survival and overall survival of patients with HCV-related HCC following curative treatment. On the basis of our results, recommendations for adjuvant interferon-based strategies to treat these patients should be considered. There is little evidence to advocate adjuvant interferon therapy for the treatment of patients with HBV-related HCC after curative treatment. Future research should clarify whether the effects of adjuvant interferon therapy are more prominent in patients with SVRs.

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## AUTHOR CONTRIBUTIONS

All authors participated in the study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript. TS Huang and PJ Chen drafted the protocol and manuscript. TS Huang and SS Yuan performed the statistical analysis.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## REFERENCES

1 Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004; 127(5 Suppl. 1): S5–S16.
2 Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; 27(9): 1485–1491.
3 Song TJ, Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. *Gastroenterology* 2004; 127(5 Suppl. 1): S248–S260.
4 Pawlik TM, Esnaola NF, Vauthey JN. Surgical treatment of hepatocellular carcinoma: similar long-term results despite geographic variations. *Liver Transpl* 2004; 10(2 Suppl. 1): S74–S80.
5 Mazzaferro V, Regalia E, Doci R *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334(11): 693–699.
6 Shimada M, Takenaka K, Gion T *et al.* Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. *Gastroenterology* 1996; 111(3): 720–726.
7 Kishi Y, Hasegawa K, Sugawara Y, Kokudo N. Hepatocellular carcinoma: current management and future development-improved outcomes with surgical resection. *Int J Hepatol* 2011; 2011: 728103.
8 Chiu JH, Wu LH, Kao HL *et al.* Can determination of the proliferative capacity of the nontumor portion predict the risk of tumor recurrence in the liver remnant after resection of human hepatocellular carcinoma? *Hepatology* 1993; 18(1): 96–102.
9 Hoshida Y, Villanueva A, Kobayashi M *et al.* Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *N Engl J Med* 2008; 359 (19): 1995–2004.
10 Kudo M. Adjuvant therapy after curative treatment for hepatocellular carcinoma. *Oncology* 2011; 81 (Suppl. 1): 50–55.
11 Yano H, Ogasawara S, Momosaki S *et al.* Growth inhibitory effects of pegylated IFN alpha-2b on human liver cancer cells in vitro and in vivo. *Liver Int* 2006; 26(8): 964–975.
12 Ikeda K, Arase Y, Saitoh S *et al.* Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000; 32(2): 228–232.
13 Kubo S, Nishiguchi S, Hirohashi K *et al.* Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001; 134(10): 963–967.
14 Lin SM, Lin CJ, Hsu CW *et al.* Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. *Cancer* 2004; 100(2): 376–382.
15 Mazzaferro V, Romito R, Schiavo M *et al.* Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006; 44 (6): 1543–1554.
16 Chen LT, Chen MF, Li LA *et al.* Long-term results of a randomized, observation-controlled, phase III trial of adjuvant interferon Alfa-2b in hepatocellular carcinoma after curative resection. *Ann Surg* 2012; 255(1): 8–17.
17 Zhang CH, Xu GL, Jia WD, Li JS, Ma JL, Ge YS. Effects of interferon treatment on development and pro-

gression of hepatocellular carcinoma in patients with chronic virus infection: a meta-analysis of randomized controlled trials. *Int J Cancer* 2011; 129(5): 1254–1264.
18 Singal AK, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2010; 32(7): 851–858.
19 Shen YC, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. *J Hepatol* 2010; 52(6): 889–894.
20 Miyake Y, Takaki A, Iwasaki Y, Yamamoto K. Meta-analysis: interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *J Viral Hepat* 2010; 17(4): 287–292.
21 Miao RY, Zhao HT, Yang HY *et al.* Postoperative adjuvant antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: a meta-analysis. *World J Gastroenterol* 2010; 16(23): 2931–2942.
22 Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; 379(9822): 1245–1255.
23 Huang TS, Shyu YC, Shih JN, Chen PJ, Yuan SS. A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis related hepatocellular carcinoma. PROSPERO 2012:CRD42012002419. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002419 (accessed 20 October 2012).
24 Abraham NS, Byrne CJ, Young JM, Solomon MJ. Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures is as good as randomized controlled trials. *J Clin Epidemiol* 2010; 63(3): 238–245.
25 Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org (accessed 18 April 2012).
26 Wells GA, Shea B, O'Connell D *et al.* The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 18 April 2012).
27 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998; 17(24): 2815–2834.
28 Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; 8: 16.
29 Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011; 342: d549.
30 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414): 557–560.
31 Ioannidis JPA, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ* 2007; 335(7626): 914–916.
32 Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg* 2002; 89(4): 418–422.
33 Miyaguchi S, Watanabe T, Takahashi H, Nakamura M, Saito H, Ishii H. Interferon therapy for hepatocellular carcinoma patients with low HCV-RNA levels. *Hepatogastroenterology* 2002; 49(45): 724–729.
34 Shiratori Y, Shiina S, Teratani T *et al.* Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003; 138(4): 299–306.
35 Nishiguchi S, Tamori A, Kubo S. Effect of long-term postoperative interferon therapy on intrahepatic recurrence and survival rate after resection of hepatitis C virus-related hepatocellular carcinoma. *Intervirology* 2005; 48(1): 71–75.
36 Sun HC, Tang ZY, Wang L *et al.* Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. *J Cancer Res Clin Oncol* 2006; 132(7): 458–465.
37 Lo CM, Liu CL, Chan SC *et al.* A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. *Ann Surg* 2007; 245(6): 831–842.
38 Ishikawa T, Higuchi K, Kubota T *et al.* Combination PEG-IFN a-2b/ribavirin therapy following treatment of hepatitis C virus-associated hepatocellular carcinoma is capable of improving hepatic functional reserve and survival. *Hepatogastroenterology* 2012; 59(114): 529–532.
39 Suou T, Mitsuda A, Koda M *et al.* Interferon alpha inhibits intrahepatic recurrence in hepatocellular carcinoma with chronic hepatitis C: a pilot study. *Hepatol Res* 2001; 20(3): 301–311.
40 Hung CH, Lee CM, Wang JH, Tung HD, Chen CH, Lu SN. Antiviral therapy after non-surgical tumor ablation in patients with hepatocellular carcinoma associated with hepatitis C virus. *J Gastroenterol Hepatol* 2005; 20(10): 1553–1559.
41 Sakaguchi Y, Kudo M, Fukunaga T, Minami Y, Chung H, Kawasaki T. Low-dose, long-term, intermittent interferon-alpha-2b therapy after radical treatment by radiofrequency ablation delays clinical recurrence in patients with hepatitis C virus-related hepatocellular carcinoma. *Intervirology* 2005; 48(1): 64–70.
42 Akamatsu M, Yoshida H, Shiina S *et al.* Sustained viral response prolonged survival of patients with C-viral hepatocellular carcinoma. *Liver Int* 2006; 26(5): 536–542.
43 Someya T, Ikeda K, Saitoh S *et al.* Interferon lowers tumor recurrence rate after surgical resection or ablation of hepatocellular carcinoma: a pilot study of patients with hepatitis B virus-related cirrhosis. *J Gastroenterol* 2006; 41(12): 1206–1213.
44 Kudo M, Sakaguchi Y, Chung H *et al.* Long-term interferon maintenance therapy improves survival in patients with HCV-related hepatocellular carcinoma after curative radiofrequency ablation. A matched

case–control study. *Oncology* 2007; 72(Suppl. 1): 132–138.
45 Jeong SC, Aikata H, Katamura Y *et al.* Effects of a 24-week course of interferon-alpha therapy after curative treatment of hepatitis C virus-associated hepatocellular carcinoma. *World J Gastroenterol* 2007; 13(40): 5343–5350.
46 Jeong S, Aikata H, Katamura Y *et al.* Low-dose intermittent interferon-alpha therapy for HCV-related liver cirrhosis after curative treatment of hepatocellular carcinoma. *World J Gastroenterol* 2007; 13(39): 5188–5195.
47 Katagiri S, Tokushige K, Yamamoto M. [Postoperative interferon therapy after resection of hepatitis C virus-related hepatocellular carcinoma]. *Nihon Shokakibyo Gakkai Zasshi* 2008; 105(6): 795–801.
48 Ikeda K, Kobayashi M, Seko Y *et al.* Administration of interferon for two or more years decreases early stage hepatocellular carcinoma recurrence rate after radical ablation: a retrospective study of hepatitis C virus-related liver cancer. *Hepatol Res* 2010; 40(12): 1168–1175.
49 Qu LS, Jin F, Huang XW, Shen XZ. Interferon-alpha therapy after curative resection prevents early recurrence and improves survival in patients with hepatitis B virus-related hepatocellular carcinoma. *J Surg Oncol* 2010; 102(7): 796–801.
50 Hagihara H, Nouso K, Kobayashi Y *et al.* Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *Int J Clin Oncol* 2011; 16(3): 210–220.
51 Tanimoto Y, Tashiro H, Aikata H *et al.* Impact of pegylated interferon therapy on outcomes of patients with hepatitis C virus-related hepatocellular carcinoma after curative hepatic resection. *Ann Surg Oncol* 2012; 19(2): 418–425.
52 European Association of the study of the liver. 2011 European Association of the Study of the Liver hepatitis C virus clinical practice guidelines. *Liver Int* 2012; 32(Suppl. 1): 2–8.
53 Ayoub WS, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. *Aliment Pharmacol Ther* 2011; 34(10): 1145–1158.

## APPENDIX 1

### SEARCH STRATEGIES FOR MEDLINE

1. Explore MeSH terms and keyword searches: hepatocellular carcinoma, hepatic tumour, liver cancer, liver tumour.
2. Explore MeSH terms and keyword searches: interferon, peginterferon, pegylated interferon, viraferonpeg, pegintron, pegasys.
3. Combine 1 and 2.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Fig. S1:** Forest plot of randomized trials comparing the recurrence-free survival of patients with viral hepatitis-related hepatocellular carcinoma treated with adjuvant interferon therapy after curative treatment with that of controls.

**Fig. S2:** Forest plot of randomized trials comparing the overall survival of patients with viral hepatitis-related hepatocellular carcinoma treated with adjuvant interferon therapy after curative treatment with that of controls.

**Fig. S3:** Forest plot of randomized trials comparing the recurrence-free survival of patients with viral hepatitis-related hepatocellular carcinoma treated with adjuvant interferon therapy after curative treatment with that of controls. The data are stratified according to the type of viral hepatitis.

**Fig. S4:** Forest plot of randomized trials comparing the overall survival of patients with viral hepatitis-related hepatocellular carcinoma treated with adjuvant interferon therapy after curative treatment with that of controls. The data are stratified according to the type of viral hepatitis.

**Fig. S5:** Forest plot of non-randomized studies comparing the recurrence-free survival of patients with viral hepatitis-related hepatocellular carcinoma treated with adjuvant interferon therapy after curative treatment with that of controls. The data are stratified according to the type of viral hepatitis.

**Fig. S6:** Forest plot of non-randomized studies comparing the recurrence-free survival of patients with sustained virological responses treated with adjuvant interferon therapy with that of controls.

**Fig. S7:** Forest plot of non-randomized studies comparing the overall survival of patients with sustained virological responses treated with adjuvant interferon therapy with that of controls.

**Fig. S8:** Funnel plot illustrating the standard error by log hazard ratio of recurrence-free survival in non-randomized studies recruited patients with viral hepatitis C-related hepatocellular carcinoma.

**Table S1:** Studies involving adjuvant interferon treatment after curative treatment of patients with viral hepatitis-related hepatocellular carcinoma that were excluded from the systematic review.

**Table S2:** Risk of bias summary: review authors' judgments regarding each risk of bias item across all the included randomized controlled trials.

**Table S3:** Study quality rating assessed according to the Newcastle-Ottawa scale for non-randomized trials included in the systematic review of adjuvant interferon treatment.